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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,333	05/24/2005	Edith Dellacherie	122536	8802

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,333	DELLACHERIE ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 28-32* is/are pending in the application.

4a) Of the above claim(s) *8 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-20 and 28-32* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Request for Continued Examination (RCE), as well as their Amendments and Remarks all of which was timely filed on 8 September 2009. Said amendments and remarks are entered on the record. The Examiner further acknowledges the following:

Claims 1-7, 9-24 and 28-32 are now pending with claim 32 being newly added and claims 21-24 remaining withdrawn from consideration. Claim 19 has been reconsidered by the Examiner and is at this time **rejoined** for consideration on the merits.

The addition of claim 32 is supported by the original claims as well as the instant disclosure.

Claim 1 alone has been amended adding the phrase "a hyaluronan-based coating composition consisting of" in order to more clearly distinguish over the applied references.

No additional claims have been cancelled.

No new matter has been added.

As such, claims 1-7, 9-20 and 28-32 now represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No Information Disclosure Statements (IDS) have been filed for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejection under 35 USC 103(a)

Applicants' remarks concerning the rejection to claims 1-7, 9-18, 20 and 28-31 under 35 USC 103(a), as being unpatentable over the combined teachings of Ottoboni et al. (WO 98/48783) in view of the machine translation of Dellacherie et al. (FR 2 794 763) and Illum (USPN 4,904,479), have been reconsidered and are **persuasive**. Specifically, Applicants remarks concerning the differences between the means for attaching the coating component to the particle as taught by Ottoboni versus the clarified recitation of the instant claim 1 are sufficient. Since the combined teachings of the references are no longer considered as reading on the base limitations, said rejection now stands **withdrawn**.

NEW OBJECTIONS/REJECTIONS

In light of Applicants' remarks, the withdrawn rejection discussed above, as well as the addition of new claims 32, the following rejections have been newly added:

CLAIM OBJECTIONS

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 30 presently depends from claim 6. Claim 6, as discussed herein, recites that the alkyl group esterified to the hyaluronic acid component of the coating, has a chain length of 18 carbon atoms (i.e. the chain length *is* 18

carbons long) [*emphasis added*]. Claim 30, recites in its dependency from claim 6, that the alkyl *chains* have alkyl chains having a length of 10 carbon atoms or greater. Thus, claim 30 is considered to not further limit the composition of claim 6, since claim 6 discusses HA with a single 18-carbon esterified chain versus claim 30 which recites HA having multiple alkyl chains of 10 or more carbons in length.

CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 13, the phrases "such as" and "for example" render the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 14 is rejected on the grounds that it depends from claim 13.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 9-13, 16-20, 28, 29, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (USPN 4,904,479).

The independent claims are directed to a particle having a core and a coating, wherein the core comprises at least one biodegradable organosoluble polymer. The coating is comprised of at least one hyaluronan or one of its derivatives. The hyaluronan-based coating is further characterized as either partially or fully encapsulating the particle as well as being chemically modified via ester or amide functional groups so as to form hydrophobic groups which interact with the polymer core (claims 1, 2, 20 and 32). Claim 3 recites that the group which is esterified to hyaluronan is a linear or branched, saturated or

unsaturated alkyl chain. Claim 29 further limits the alkyl group of claim 3 such that it is interrupted with one or more hetero atom(s). "Hetero atoms" are defined by Applicants as including sulfur, oxygen and/or nitrogen atoms (see pg. 4, lines 27-29). Claims 9-11 and 28 recite limitations to the biodegradable organosoluble polymer, such as polylactic acid, polyglycolic acid and copolymers thereof and that it is a natural biodegradable polymer (claim 28).

The invention of Illum is directed to a drug delivery system comprising an active drug as a suspension of colloidal particles, wherein each particle is coated with a material which provides a hydrophilic coat (claim 1). Though the examples and teachings of Illum are primarily directed to a model where the core particles comprise polystyrene and the coating material comprises poloxamer, it is expressly taught and suggested that other materials may be used to accomplish practiced invention. Of particular note, Illum teaches that the core particles may include polylactides, polyglycolides and mixtures thereof (e.g. copolymers), whereas coating materials which would provide the same effect as the poloxamers include those which may be esterified to produce suitable hydrophilic and hydrophobic domains. It is further suggested that polymers which may undergo such a modification include hyaluronic acid (col. 10, lines 25-41). The hydrophobic domains, which are taught as preferably including polyoxypropylene in addition to other hydrophobic groups can be modified into polymer chains, for example by way of esterification of maleic acid groups (col. 2, lines 31-34). Though maleic acid is an uninterrupted aliphatic dicarboxylic acid compound (e.g. linear alkyl), the continued esterification of multiple

maleic acid groups, as suggested by Illum, would result in an aliphatic maleic acid polymer interrupted by oxygen atoms.

Claims 12 and 13 recite that the particle core further comprises at least one biological active, such as proteins. Claim 16 recites that the particle core further comprises up to 95% by weight of an active substance.

Illum expressly teaches and suggests that the particle core may be alternatively comprised of monomers and copolymers of PLA and/or PGA. It is further taught and suggested that the polymer mixture may also include the protein albumin (col. 10, lines 25-32). Though there is no percentage of albumin which is expressly taught within the core, it is the position of the Examiner that since the protein can be present in the particle core is suggestion enough that it would be present in an amount greater than 0%, which expressly reads on the instant limitation of *up to* 95% by weight.

Claims 17 and 31 each further limit the composition of claim 1 with regards to its particle size. Claim 17 recites a particle size range of 50 nm (0.05 microns) to 600 microns, whereas claim 31 recites a range of 80 nm to 230 microns. Claim 18 recites that the particle is a nanoparticle, whereas claim 19 recites the particle as a microparticle. Per Applicants' disclosure, a nanoparticle ranges in size from 1-1,000 nm, whereas a microparticle ranges from 1,000 nm to several thousand microns (see pg. 9, lines 8-11).

Illum teaches expressly teaches the instantly claimed nanoparticle sizes (e.g. 50-60 nm) in the Examples (see for example, Example 1, col. 5, lines 20-21). Again though the practiced invention is directed preferably to polystyrene core particles, as discussed above,

the polymer core may be substituted with the aforementioned biodegradable polymers. Regarding Applicants' instant claims directed to the larger microparticle ranges, Illum also discusses conducting performing mouse peritoneal macrophage studies where larger microspheres having a 5.25 micron diameter are used (see e.g. col. 3, lines 40-47).

Thus, in view of the express teachings provided by Illum, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have arrived at a particle composition as instantly claimed. Though the practiced invention of Illum is directed primarily to polystyrene core particles encapsulated with a polyoxyethylene-polyoxypropylene based coating, the ordinarily skilled artisan would have been highly motivated to derived a composition, for example, of a PLA-PGA copolymer core having an esterified hyaluronic acid coating.

Based on the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, alone or in combination, especially in the absence of evidence to the contrary.

Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Illum et al. with respect to claims 1-3, as set forth above, and della Valle et al. (USPN 4,851,521) in further view of McMurry (*3rd Ed.*; 1992).

The limitations of claims 1-3 are discussed above. Claim 4 recites that the hyaluronic acid of claims 1-3 has esterified to it an alkyl chain comprising five or more

carbon atoms. Claim 5 further narrows the chain length to 15-20 carbon atoms and further recites that the alkyl group has a degree of esterification of at most 15%. Claim 6 further narrows claim 5 to a length of 18 carbon atoms. Claim 7 further limits the composition of claim 6 to a degree of esterification of less than 7%.

The teachings of Illum are discussed above. Of particular note is that the practiced invention teaches and suggests the use of esterified hyaluronic acid as a coating composition over core particles composed of homo- or copolymers of PLA and/or PGA. However, Illum does not expressly elaborate on the alkyl groups which are esterified to HA except to suggest that maleic acid groups may be used in the esterification reaction. This deficiency further includes the instantly claimed alkyl chain length and the degree of esterification properties.

The invention of della Valle et al. is directed to the preparation and use of the esters of hyaluronic acid in which all or a portion of which of the carboxylic groups of the acid are esterified (Abstract). The esterified alcohol-based hyaluronic acids are taught as being applicable in the pharmaceutical field as carriers of pharmaceutical active agents and or carrying vehicles (col. 5, lines 1-5). Alcohols of the aliphatic series to be used as esterifying components of the carboxylic groups of HA according to the invention include those with a maximum of 34 carbon atoms, which may be either saturated or unsaturated as well as optionally substituted with various sulfur-based (e.g. mercaptan), nitrogen-based (e.g. amine) or oxygen-based (e.g. hydroxyide) components (col. 5, lines 27-34). The aforementioned alcohols are further taught as optionally being interrupted in the carbon atom chain by heteroatoms such as oxygen, nitrogen and sulfur atoms (col. 5, lines 48-50).

Though della Valle does generally discuss the degree of esterification of HA with regards to the aforementioned alcohol components (col. 8, lines 18-26), specific degrees of esterification are not, such as those which are instantly claimed.

However, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have prepared esterified forms of hyaluronic acid as taught by della Valle and applied them as coating compounds to the PLA and/or PGA copolymer core particles of Illum. The ordinarily skilled artisan would have been highly motivated to do this particularly in view of the aforementioned teaching of Illum where PLA/PGA cores are coated with esterified forms of HA. Regarding Applicants limitations of creating hydrophobic groups in order to hydrophobically "anchor" the coating to the particle (i.e. control the degree of esterification), della Valle further teaches that the degree of esterification of the carboxylic groups of HA using an alcohol (e.g. stearic alcohol) is dependent on the desired end-use properties, such as control of hydrophilicity and hydrophobicity. It is further taught that increasing or decreasing the degree of esterification of HA will control its solubility in water (col. 8, lines 18-26). Thus, in view of the combined teachings, it is the position of the Examiner that it would have also been well within the purview of the skilled artisan to employ an esterification reaction (e.g. Fischer esterification reaction) in order to arrive at the desired degree of esterification and thus arrive desired number of hydrophobic groups required to anchor the coating to the particle core (see e.g. pp.803-804 of McMurry; 1992). It follows that the reacting HA in this fashion is a result-effective means for optimizing hyaluronic acid that would have been obvious for a person of ordinary skill in the art to employ. Thus, absent some demonstration of

unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

Based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Illum et al. with respect to claims 1, 12 and 13 as set forth above, and Lee et al (USPN 5,753,234).

The limitations to claims 1, 12 and 13 are discussed above. Claim 14 further limits the composition of claim 13 such that the encapsulated active substance is chosen from glucosamine, hyaluronic acid, chondroitin sulfate and mixtures thereof. Claim 15 further limits the "synthetic active substance" limitation of claim 12 reciting that it comprises a synthetic medicinal product such as anti-inflammatory compounds or antibiotics.

The teachings of Illum are discussed above. Again, of particular note are the teachings whereby the particles prepared by Illum comprise a biodegradable core (e.g. PLA and/or PGA homo- and/or copolymers) and wherein the coating applied may be an esterified form of hyaluronic acid (col. 10, lines 25-41). It should also be noted that the size of particles used taught by the Illum reference range from as small as 50 nm to as large as 5.25 microns. The invention of Illum is deficient in so much as there is no express teaching that

the active substance within the PLA/PGA core particle is any of those which are instantly claimed. However, the teachings of Lee et al. rectify this deficiency.

Lee et al. is directed to the preparation of microparticles which range in size from 0.5-300 microns and which are prepared by dissolving one or more antigens in an aqueous solution and removing the residual water to form a core particle. Said active core particles are then coated with a biodegradable polymer (Abstract). Exemplary water-soluble substances are taught as including hyaluronic acid (col. 6, lines 2-5). Exemplary antigens are expressly taught as including antibiotics, antiviral agents and immunizing substances (col. 5, lines 46-55). Exemplary hydrophobic used to encapsulate the cores include PLGA, PGA and PLA, where PLGA and PLA are preferred (col. 6, lines 30-36). The biodegradable polymer is further taught as being used in an amount which ranges as high as 100-times the individual particle weight (col. 6, lines 23-25). It is thus the position of the Examiner that the particles which are prepared by Lee expressly teach the instantly claimed biodegradable polyester core which further encapsulates one or more of the active ingredients of recited in claims 14-15.

Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have coated the medicated PLA/PGA microparticle prepared by Lee using a hyaluronic acid-based coating composition as taught by Illum in order to produce the instantly claimed composition. The ordinarily skilled artisan, recognizing that the Illum teachings are directed to using an HA-based coating to encapsulate a biodegradable polyester-based core particle, would also recognize that the Lee invention prepares the same type and size of particles which are coated by Illum. The only

exception is that the particles prepared by Lee further encapsulate an active substance. Given that both of the references are directed to the formation of pharmaceutical delivery formulations, the ordinarily skilled artisan would be motivated to modify the teachings of Illum with the particle of Lee in order to control the release of the active ingredient.

Thus, based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

All claims have been rejected; no claims are allowed.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information

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/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615